Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Methods

Discontinuation Criteria

Remdesivir treatment was to be discontinued in any patient experiencing a serious adverse event or an adverse event of grade 3 severity or higher deemed to be related to remdesivir, an elevation in ALT greater than 5 times the upper limits of normal (ULN), an elevation in ALT more than 3 times the ULN, an elevation in total bilirubin more than 2 times the ULN, or a decrease in creatinine clearance to less than 30 mL/min.

Probability Distribution of the Ordinal Scale at Day 14

Our sample size calculation was based on the assumption that the probability distribution of the ordinal scale at day 14 in the 5-day dosing group would be as follows: 38% of patients would have been discharged from the hospital, 20% would be hospitalized without requiring medical care or supplemental oxygen, 16% would be hospitalized requiring ongoing medical care but no supplemental oxygen, 13% would be hospitalized requiring low-flow oxygen, 7% would be hospitalized requiring non-invasive ventilation or high-flow oxygen, 4% would be hospitalized on invasive mechanical ventilation, and 2% would have died.

Missing Data for the Primary Endpoint

This analysis considered patients who were discharged prior to Day 14 to have a clinical status of "Not Hospitalized' on Day 14 and patients who died prior to Day 14 to have a clinical status of “Death” on Day 14. There were 17 patients who had not died, had not been discharged, and did not have a clinical status reported on Day 14. Their last available clinical status was used to impute clinical status on Day 14. Of these 17 patients, 1 was enrolled in error and was discontinued from study drug on Day 2, and 16 were transferred to another facility before Day 14.

Supportive Analysis for the Primary Endpoint

The p-value for overall test (ie, score test) of the proportional odds assumption was 0.0017 indicating that the proportional odds assumption was not supported by the data for at least one covariate in the model. Separate tests of proportionality for each of the two covariates (ie,

treatment and baseline clinical status) produced using PROC LOGISTIC suggested that the proportional odds assumption held for treatment (p=0.1244), but not for baseline clinical status (p=0.0028). The stratified Wilcoxon rank sum test was prespecified to compare the treatment groups in the case that the proportional odds assumption was not met. The p-value from the Wilcoxon rank sum test stratified by baseline clinical status comparing Day 14 clinical status between treatment groups was 0.144.

Several post-hoc sensitivity analyses were performed for the proportional odds model. Analysis of day 14 outcomes without baseline clinical status adjustment favored the 5-day treatment group, while adjusting for baseline clinical status as a categorical variable was similar to the result derived from the prespecified method using baseline status as a continuous variable (Supplementary Table S2). Finally, imputation of patients transferred out of the hospital and lost-to-follow-up prior to day 14 (n=7) as deaths produced a similar odds ratio as the primary analysis (Supplementary Table S2).

Other analyses were performed to support the primary analysis, and results confirmed the conclusion of no significant difference between groups. These analyses included time to ≥2-point clinical improvement, recovery, modified recovery, as well as the proportion of patients with clinical improvement, recovery, and modified recovery at Days 5, 7, 11, and 14.

Analysis of Adverse Events and Endpoints of Interest

For adverse events and secondary endpoints related to proportions, we constructed the baseline stratum-weighted difference in proportions and 95% CIs based on Mantel–Haenszel proportion adjusted by baseline clinical status. Time-to-event endpoints were analyzed using competing risk models, where the competing risk was death.

For time to clinical improvement, time to recovery, and time to modified recovery, the hazard ratio and its 95% confidence interval (CI) were estimated from cause-specific proportional hazard model including treatment and baseline clinical status as covariates. The proportional hazards assumption was supported by the data; p-values for treatment and baseline clinical status were > 0.05 by supremum test for proportional hazards assumption for the three endpoints of interest.

Univariate and Multivariate Analyses to Identify Baseline Predictors for Time to Clinical Improvement

Univariate Analysis: For each baseline predictor, Gray's Test (1988) a non-parametric test, was used to compare the equality of the cumulative incidence functions estimated for each category of this baseline predictor. This test does not require proportional hazards assumption and independent censoring assumption and is commonly used when analyzing competing risk data. The baseline predictors under consideration included 11 demographic and baseline characteristics variables (age, sex, race, ethnicity, region, baseline clinical status, baseline body mass index, baseline ALT, baseline AST, duration of hospitalization prior to first dose of remdesivir, and duration of Covid-19 symptoms prior to first dose of remdesivir); and 10 medical history conditions (asthma, cancer, cardiovascular disease, liver, COPD, diabetes, HIV AIDs, hypertension, immunologic disease, and renal disease); and 5 concomitant medications (azithromycin, biologic medications, HIV PI drugs, hydroxychloroquine, and ribavirin). Baseline predictors with p-value less than 0.2 from Gray's test were reported in Supplementary Table S3.

Multivariate Analysis: Stepwise model selection was used to identify baseline predictors simultaneously associated with time to clinical improvement using cause-specific proportional hazard model, which included the baseline predictors selected from the univariate analysis (p-value <0.2). The significance level for model entry and retention was specified as 0.05 and 0.10. The final multivariate model ultimately included treatment and five of these selected baseline predictors (baseline clinical status, race, age, region, and biologic medication use) . Hazard ratio, its 95% confidence interval, and p-value for the multivariate model were reported in Supplemental Table S4.

Table S1. Ordinal Scale of Clinical Status

Score	Clinical Status	Scale Used in ACTT Trial
1	Death	8
2	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	7
3	Hospitalized, on non-invasive ventilation or high-flow oxygen devices	6
4	Hospitalized, requiring low-flow supplemental oxygen	5
5	Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (related or not to Covid-19)	4
6	Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than that specified in the protocol for remdesivir administration)	3
7	Not hospitalized	1-2

The ordinal scale used in our trial was based on that developed for severe influenza requiring hospitalization.[1,2] The recently published ACTT trial[3] of remdesivir vs placebo in patients with Covid-19 used an inversion of this scale recommended by WHO in a guideline[4] issued after our study design had been finalized (see Table above).

1. Davey RT Jr, Fernández-Cruz E, Markowitz N, et al. Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): a double-blind, randomised, placebo-controlled trial. Lancet Respir Med 2019;7:951–63.

2. Peterson RL, Vock DM, Powers JH, et al. Analysis of an ordinal endpoint for use in evaluating treatments for severe influenza requiring hospitalization. Clin Trials 2017:14:264-276.

3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — preliminary report. N Engl J Med 2020.

4. World Health Organization. WHO R&D blueprint novel Coronavirus COVID-19 therapeutic trial synopsis. Available at: https://www.who.int/publications-detail/covid-19-therapeutic-trial-synopsis.

Table S2. Post-hoc Sensitivity Analyses

	RDV for 10 Days/RDV for 5 Days Odds Ratio (95% CI)†
Adjusted for Baseline Clinical Status (primary endpoint)	0.75 (0.51, 1.12)
Unadjusted for Baseline Clinical Status	0.67 (0.46, 0.97)
Adjusted for Baseline Clinical Status as a Nominal Categorical Variable	0.74 (0.50, 1.11)
Discharges prior to Day 14 and lost to follow-up imputed as death at Day 14 (adjusted for baseline clinical status)*	0.78 (0.53, 1.15)

Note: Odds ratios less than 1 indicate lower odds of being in a better category for the 10-day group compared to the 5-day group, ie, results are in favor of 5-day group.

*216/223 patients were discharged prior to Day 14 and were imputed as "Not Hospitalized" on Day 14 for the primary analysis. Information from follow-up visit on Day 28 confirmed that all but 7 of the 216 patients had a status of "Not Hospitalized" on Day 14. The remaining 7 were lost to follow-up and did not attend the Day 28 follow-up visit. In this sensitivity analysis these 7 patients were treated as "Death" on Day 14.

†Proportional odds assumption held for treatment, but not for baseline clinical status. The common odds ratio was reported for treatment comparison only.

Table S3. Baseline Predictors of Time to Clinical Improvement (with p-values <0.2)

Baseline Predictors	Categories	Patients Achieving Clinical Improvement (Events) N (%)	Patients who Died Before Achieving Clinical Improvement (Competing Risks) N (%)	Patients Not Achieving Clinical Improvement (Censors) N (%)
Age*	<65	175 / 229 (76%)	13 / 229 (6%)	41 / 229 (18%)
	≥65	81 / 168 (48%)	31 / 168 (18%)	56 / 168 (33%)
Sex	Female	102 / 144 (71%)	10 / 144 (7%)	32 / 144 (22%)
	Male	154 / 253 (61%)	34 / 253 (13%)	65 / 253 (26%)
Race*	Asian	26 / 45 (58%)	4 / 45 (9%)	15 / 45 (33%)
	Black	37 / 44 (84%)	3 / 44 (7%)	4 / 44 (9%)
	White	171 / 276 (62%)	34 / 276 (12%)	71 / 276 (26%)
Region*	Ex-Italy	220 / 320 (69%)	25 / 320 (8%)	75 / 320 (23%)
	Italy	36 / 77 (47%)	19 / 77 (25%)	22 / 77 (29%)
Obesity	Non-Obese	135 / 226 (60%)	24 / 226 (11%)	67 / 226 (30%)
	Obese	115 / 163 (71%)	19 / 163 (12%)	29 / 163 (18%)
Baseline clinical status*	IMV or HFNC/NIPPV	47 / 122 (39%)	33 / 122 (27%)	42 / 122 (34%)
	Low Flow O_2 or Room Air	209 / 275 (76%)	11 / 275 (4%)	55 / 275 (20%)
AST	≤43 U/L	140 / 198 (71%)	23 / 198 (12%)	35 / 198 (18%)
	>43 U/L	113 / 191 (59%)	20 / 191 (10%)	58 / 191 (30%)
Cardiovascular disease	Absent	191 / 283 (67%)	23 / 283 (8%)	69 / 283 (24%)
	Present	65 / 114 (57%)	21 / 114 (18%)	28 / 114 (25%)
Hypertension	Absent	136 / 199 (68%)	17 / 199 (9%)	46 / 199 (23%)
	Present	120 / 198 (61%)	27 / 198 (14%)	51 / 198 (26%)
Received biologic medication*	No	243 / 367 (66%)	42 / 367 (11%)	82 / 367 (22%)
	Yes	13 / 30 (43%)	2 / 30 (7%)	15 / 30 (50%)
Received hydroxychloroquine	No	192 / 288 (67%)	34 / 288 (12%)	62 / 288 (22%)
	Yes	64 / 109 (59%)	10 / 109 (9%)	35 / 109 (32%)

Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical improvement is defined as ≥2-point improvement from the baseline clinical status or discharged alive.
Subjects who died before achieving clinical improvement were considered to have experienced a competing event.
Subjects not achieving clinical improvement at the last assessment were censored on the day of the last clinical assessment.
*Selected by stepwise selection using cause-specific proportional hazard model with entry significance level = 0.05 and stay significance level = 0.10.

Table S4. Multivariate Analysis of Time to Clinical Improvement by Cause-Specific Hazard Model

Baseline Predictors	Comparison	Hazard Ratio	95% CI
Baseline Clinical Status	Low Flow O_2 or Room Air vs. IMV or HFNC/NIPPV	2.157	(1.502, 3.099)
Race	Black vs. Asian	3.804	(2.280, 6.347)
	White vs. Asian	2.450	(1.599, 3.755)
Age	< 65 vs. ≥65	1.933	(1.463, 2.554)
Received Biologic Medication	Absent vs. Present	2.699	(1.494, 4.876)
Region	Ex-Italy vs. Italy	1.592	(1.068, 2.373)
Treatment	5 Days vs. 10 Days	1.195	(0.920, 1.552)

Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical improvement is defined as ≥2-point improvement from the baseline clinical status or discharged alive.
Subjects who died before achieving clinical improvement were considered to have experienced a competing event.
Subjects not achieving clinical improvement at the last assessment were censored on the day of the last clinical assessment.
Cause-specific hazard ratio and its 95% CI were estimated from cause-specific proportional hazard model including treatment and all other selected baseline predictors as covariates.

Table S5: Adverse Events by Days 1-5 and Days 6-10 by Treatment Arm

	Remdesivir for 5 Days		Remdesivir for 10 Days	
	Days 1 to 5 (N=200)	**Days 6 to 10* (N=149)**	**Days 1 to 5 (N=197)**	**Days 6 to 10* (N=150)**
Adverse events	120 (60%)	51 (34%)	122 (62%)	66 (44%)
Serious adverse events	31 (15%)	10 (7%)	45 (23%)	18 (12%)
Adverse events ≥ Grade 3	46 (23%)	15 (10%)	62 (31%)	21 (14%)
Adverse events leading to study drug discontinuation	9 (4%)	NA	14 (7%)	6 (4%)
Drug-related serious adverse events	3 (1%)	0	4 (2%)	0 (0%)
Drug-related adverse events ≥ Grade 3	8 (4%)	0	8 (4%)	2 (1%)

*The denominator for adverse events Days 6 to 10 is patients who had a non-missing clinical status on Day 6 and who had not died or had not been discharged alive on Day 6.

Table S6: Adverse Event Outcomes with Baseline Adjustment

	Remdesivir for 5 days (N=200)	Remdesivir for 10 days (N=197)	Difference (95% CI)	Baseline-adjusted difference* (95% CI)
Any adverse event	141 (70)	145 (74)	3.1 (-5.8, 12.0)	0.8 (-8.1, 9.6)
Grade ≥3 adverse event	61 (30)	84 (43)	12.1 (2.0, 21.6)	8.6 (-0.5, 17.6).
Adverse event leading to discontinuation of treatment	9 (4)	20 (10)	5.7 (0.4, 11.3)	4.8 (-0.5, 10.1)
Any serious adverse event	42 (21)	68 (35)	13.5 (3.5, 22.3)	10.8 (2.4, 19.2)

*Baseline-adjusted differences and its CI were estimated from the Mantel-Haenzel proportions adjusted by baseline clinical status.

Figure S1. Oxygen-Support Status at Baseline and at Day 14

			Patients in Oxygen-Support Group at Baseline, N (%)							
			5-day course of remdesivir (N=192)*				10-day course of remdesivir (N=188)*			
			Invasive (N=4)	Noninvasive (N=49)	Low-flow oxygen (N=107)	Ambient air (N=32)	Invasive (N=8)	Noninvasive (N=58)	Low-flow oxygen (N=102)	Ambient air (N=20)
			2	3	4	5/6	2	3	4	5/6
No. of Patients In Oxygen-Support Group at Day 14 (%)	Death	1	1 (25)	8 (16)	5 (5)	2 (6)	4 (50)	13 (22)	2 (2)	2 (10)
	Invasive	2	2 (50)	6 (12)	8 (7)	0	3 (38)	19 (33)	9 (9)	1 (5)
	Non-invasive	3	0	7 (14)	2 (2)	0	0	4 (7)	3 (3)	1 (5)
	Low-flow oxygen	4	1 (25)	7 (14)	8 (7)	2 (6)	0	5 (9)	6 (6)	0
	Ambient air	5/6	0	2 (4)	11 (10)	0	0	2 (3)	8 (8)	3 (15)
	Discharged	7	0	19 (39)	73 (68)	28 (88)	1 (12)	15 (26)	74 (73)	13 (65)
	Improvement		**1 (25)**	**28 (57)**	**84 (79)**	**28 (88)**	**1 (12)**	**22 (38)**	**82 (80)**	**13 (65)**

*Patients with non-missing values at day 14.